J = 4.7), 4.92 (s, 1), 5.21 (s, 1); ^{13}C NMR (C_6D_6) δ 23.01, 23.12, 26.30, 28.03, 29.97, 31.60, 33.16, 35.44, 42.58, 45.44, 47.07, 47.27, 47.79, 63.09, 105.37, 158.01, 212.56. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.99; H, 10.36; N, 5.40.

(±)-Fawcettimine (7). Ozone was bubbled through a −78 °C solution of the perchlorate salt of aminoalkene **54** (58 mg, 0.16 mmol) in methanol (1.6 mL) and CH_2Cl_2 (1.6 mL) until a blue color developed. The solution was allowed to stand at −78 °C for 5 min, and dimethyl sulfide (1 mL) was added. The colorless solution was warmed to room temperature, allowed to stand for 4 h, and concentrated under reduced pressure. The resulting semicrystalline material was dissolved in chloroform (or deuteriochloroform) (5 mL), washed with saturated $NaHCO_3$ (5 × 3 mL), and dried ($MgSO_4$). After standing for 3 days, ^1H NMR shows the product to be completely converted into fawcettimine. Concentration under reduced pressure gave 41 mg (95%) of fawcettimine as a white solid: mp 87–90 °C. The IR spectra obtained for this sample was identical with that of an authentic sample of fawcettimine: IR ($CHCl_3$) 1735, 1465, 1415, 1385, 1360, 1340, 1325, 1290, 1255, 1150, 1105, 1060, 1030, 980, 915, 890, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3, J = 6.3), 1.36–1.43 (comp, 2), 1.46–1.55 (comp, 2), 1.63 (dm, 1, J = 14.1), 1.84 (m, 1), 1.90–1.99 (comp, 3), 2.00–2.28 (comp, 7), 2.62 (dd, 1, J = 13.8, 17.7), 2.73 (ddd, 1, J = 4.0, 6.1, 14.3), 2.90 (dd, 1, J = 5.5, 14.7), 3.25 (td, 1, J = 4.2, 14.2), 3.53 (ddd, 1, J = 3.9, 9.4, 14.3), 3.90 (b, 1); ^{13}C NMR ($CDCl_3$) δ 21.792 (3), 22.120 (2), 23.693 (1), 28.004 (2), 28.214 (2), 31.844 (2), 35.569 (2), 41.823 (2), 43.229 (1), 43.741 (2), 48.201 (0), 50.114 (2), 53.604 (2), 60.071 (1), 219.833 (0). The hydrobromide salt, recrystallized from EtOH–acetone, mp 210–212 °C, had spectra identical with an authentic sample of fawcettimine hydrobromide: IR ($CHCl_3$) 3350, 3170, 2630, 1745, 1610, 1465, 1415, 1360, 1310, 1295, 1275, 1175, 1160, 1145, 1105, 1050, 980, 935, 915, 900, 890, 875, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, 3, J = 6.5), 1.46 (ddd, 1, J = 5.6, 13.8, 14.3), 1.63 (ddd, 1, J = 2.3, 2.5, 14.6), 1.74 (ddd, 1, J = 1.7, 1.8, 14.3), 1.78–1.95 (comp, 5), 2.05–2.24 (comp, 5), 2.31–2.42 (comp, 2), 2.58 (dd, 1, J = 13.1, 17.6), 2.76 (bd, 1, J = 13.3), 3.00 (ddd, 1, J = 3.7, 7.8, 13.6), 3.18 (dd, 1, J = 5.1, 14.2), 3.56 (td, 1, J = 4.3, 14.2), 4.14 (ddd, 1, J = 4.0, 8.7, 13.6), 6.0 (b, 1), 10.1 (b, 1); ^{13}C NMR ($CDCl_3$) δ 18.916 (2), 21.335 (3), 23.759 (1), 23.864 (2), 26.576 (2), 31.132 (2), 33.291 (2), 39.779 (2), 41.040 (2), 43.088 (1), 47.574 (0), 51.075 (2), 55.263 (2), 58.972 (1), 95.947 (0), 216.382 (0).

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Registry No. (±)-**7**, 118892-07-2; (±)-**7**·HBr, 103498-99-3; (±)-**9**, 103616-04-2; (±)-**14**, 69060-78-2; (±)-**14** (2-chloro deriv), 71523-91-6; **15**, 83378-96-5; (±)-**16** (isomer 1), 118892-12-9; (±)-**16** (isomer 2), 118892-29-8; (±)-**17** (isomer 1), 118892-13-0; (±)-**17** (isomer 2), 118892-30-1; (±)-**18** (isomer 1), 118892-14-1; (±)-**18** (isomer 2), 118892-31-2; (±)-**19**, 118892-15-2; (±)-**22**, 103498-91-5; (±)-**23**, 118892-16-3; (±)-**24**, 118892-17-4; (±)-**25**, 103498-92-6; **26**, 56069-39-7; (±)-**27**, 118892-18-5; (±)-**28**, 118892-19-6; **30**, 118892-20-9; (±)-**31**, 118892-21-0; (±)-**32**, 118892-22-1; (±)-**33**, 118892-23-2; (±)-**35**, 103498-93-7; (±)-7β-**35**, 103498-94-8; (±)-**36**, 118892-24-3; (±)-7β-**36**, 118892-32-3; (±)-**37**, 118892-25-4; (±)-**38**, 118892-26-5; (±)-1α-**39**, 119006-96-1; (±)-1β-**39**, 118892-27-6; (±)-**42**, 103498-95-9; (±)-**43**, 103498-96-0; (±)-**43** (ketone), 118949-23-8; (±)-**44**, 118892-08-3; (±)-**45**, 103498-97-1; (±)-**46**, 118892-09-4; (±)-**46** (ketone), 118892-10-7; (±)-**47**, 103499-00-9; (±)-**47** (ketone), 103499-01-0; (±)-**48**, 118892-11-8; (±)-**49**, 103616-03-1; (±)-**54**, 103498-98-2; (±)-**56**, 119064-90-3; (±)-**57**, 118892-28-7; (±)-**59**, 74111-25-4; (±)-**60**, 118949-24-9; CH_2=CH-CH_2Br, 106-95-6; $BrCH_2COC_6H_4$-4-OMe, 2632-13-5.

Supplementary Material Available: Experimental procedures for the preparation of three compounds used in the proof of stereochemistry of amino diol **35**, single-crystal X-ray data for one of these compounds and for fawcettimine hydrobromide, detailed peak assignments for fawcettimine and fawcettimine hydrobromide, and details of the molecular mechanics investigation (35 pages). Ordering information is given on any current masthead page.

Total Synthesis Establishing the Correct Structures of Robustadials A and B. Reinterpretation of NMR Data

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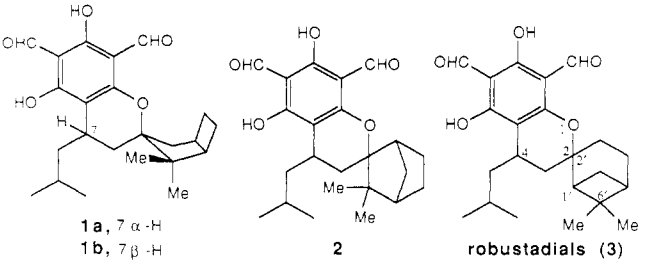
A total synthesis from (+)-nopinone establishes as **10f** and **11f** respectively the structures, including absolute stereochemistry, for robustadials A and B, natural products isolated from the antimalarial Chinese herbal medicinal extract of *Eucalyptus robusta* leaves. The ^1H and ^{13}C NMR spectral assignments for robustadial B dimethyl ether (**11e**) are examined in detail. It is then shown that the nuclear Overhauser enhancement data interpreted originally to support **1b** as the structure for this ether are actually consistent with both structures **1b** and **11e**.

An urgent need for the identification and total synthesis of new antimalarials inspired a persistent quest to unravel the elusive structures of robustadials A and B, natural products isolated from the antimalarial Chinese herbal medicinal extract of *Eucalyptus robusta* leaves.[1] The original presumption of bicyclo[3.2.0]heptyl structures **1a** and **1b** robustadials A and B, respectively,[2] was refuted by total synthesis.[3] A prenylphenol–terpenoid biogenesis



seemed likely since the aromatic acetogenin–isopentyl portion proposed for the robustadials is identical with that found in the euglobals, a family of biologically active compounds isolated from the buds and leaves of *Eucalyptus globulus*.[4] Generally the remaining terpenoid

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(2) Xu, R.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734. Complete ^{13}C NMR spectra for robustadial A and B dimethyl ethers were kindly provided by Professor Snyder.

(3) (a) Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1311. (b) Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Org. Chem.* **1988**, *53*, 3673.

0022-3263/89/1954-1562$01.50/0

portion of the euglobals corresponds to known terpenes or sesquiterpenes. The observation of major fragments corresponding to ethylene and C_8H_{11} in the mass spectrum of robustadials contributed to the original choice of a bicyclo[3.2.0]heptyl structure for the robustadials since retro-Diels–Alder fragmentation of the benzopyran ring in **1** and cleavage of the cyclobutane ring would produce ethylene and a C_8H_{11} fragment. Since mass spectral fragmentation of camphene generates similar major fragments, camphane analogues **2** of **1** were examined but shown by total synthesis also not to correspond with the natural products.[5]

Although perhaps less evident, generation of ethylene and C_8H_{11} during the mass spectral fragmentation of pinane derivatives **3** is virtually inevitable since cationic rearrangement in the mass spectrometer of the pinane segment to produce a camphane structure finds analogy in solvolytic rearrangements of pinanes.[7] Furthermore, *E. robusta* leaves yield an oil consisting "largely of pinene".[8] Therefore we postulated[5] that robustadials are pinane derivatives **3** which arise by addition of a prenylphenol moiety derived from the natural product grandinol[6] to the C=C bond of β-pinene.

Results and Discussion

Total Synthesis. Robustadial A and B dimethyl ethers were assembled from (+)-nopinone and 2,4-dimethoxy-6-hydroxyacetophenone (**4**) as outlined in Scheme I.[9] The ^1H and ^{13}C NMR[2] spectra of **10e** and **11e** are identical with those of samples prepared by methylation of natural robustadials A and B, respectively. The stereostructures of **6–11** were established by a single-crystal X-ray analysis on **11b**.[9] Further, a comparison of optical rotations and CD spectra (Figure 1) of **10e** and **11e** with those of naturally derived robustadials showed that the absolute configurations of the (+)-nopinone-derived products are identical with those of the natural products. Therefore, the absolute stereostructures of robustadials A and B correspond to **10f** and **11f**, respectively.

Spectral Analysis of Robustadial B. For noncrystalline substances, modern FT-NMR techniques are especially important to characterize complex organic structures without the aid of X-ray crystal analysis. The first attempt to determine the molecular architecture of robustadial B relied on spectroscopic methods, especially two-dimensional NMR and nuclear Overhauser enhancement (NOE) techniques.[2] NOE experiments are especially useful for revealing spatial proximity between atoms separated by many bonds or by barriers such as quaternary carbons which preclude vicinal coupling of hydrogen atoms between regions of the molecule separated by the quaternary atom. Nevertheless, the frequency of erroneous structural conclusions[2,10] calls for an investigation of the pitfalls of non-X-ray methods for molecular structure determination. To glean insights from the incorrect conclusion that robustadial B has a bicyclo[3.2.0]heptyl structure **1b**, we first unambiguously establish ^1H and ^{13}C NMR spectral assignments for robustadial B dimethyl ether (**11e**).

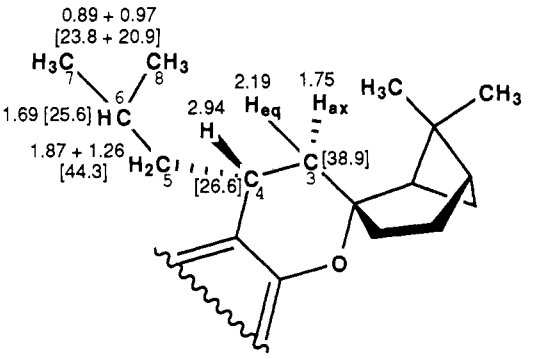
Assignments of the ^1H and ^{13}C resonances of the pyran ring, isobutyl, and pinane moieties of **11a** and **11e** are summarized in Table I. These assignments were facilitated by HETCOR spectra for **11a** which correlated all ^1H resonances with the corresponding ^{13}C resonances in **11a** and by analogy in **11e** presuming that the change from

Table I. ^1H and ^{13}C Resonances for Robustadial Dimethyl Ether (11e) and the Corresponding Resonances[a] for 11a

position[b]	^{13}C	^1H[c]
3	38.9 [40.4] (t)	H_{ax}, 1.75 [1.66] (dd, J = 15, 6.9) H_{eq}, 2.19 [2.17] (dd, J = 15, 6.9)
4	26.6 [26.6] (d)	H, 2.94 [2.86] (dddd, J = 10.0, 7.0, 6.7, 3.0)
5	44.3 [44.2] (t)	H, 1.26 [1.21] (ddd, J = 14.6, 10.8, 4.3) H, 1.87 [1.88] (ddd, J = 14.6, 11.0, 3.3)
6	25.6 [26.0] (d)	H, 1.69 [1.70] (qqdd, J = 6.8, 6.8, 11.0, 4.3)
7	23.8 [24.1] (q)	3 H, 0.89 [0.89] (d, J = 6.8)
8	20.9 [21.3] (q)	3 H, 0.97 [0.98] (d, J = 6.8)
6′-CH_{3eq}	23.4 [23.5] (q)	3 H, 1.00 [1.03] (s)
6′-CH_{3ax}	27.2 [27.3] (q)	3 H, 1.27 [1.25] (s)
1′	50.6 [50.6] (d)	H, 2.22 [2.20] (apparent t, J = 6.8)
2′	84.8 [81.0] (s)	
3′	28.1 [27.6] (t)	2 H, –[d] [1.79 and 1.83]
4′	24.7 [24.9] (t)	2 H, –[d] [1.81 and 1.90]
5′	40.3 [40.6] (d)	H, 1.96 [1.93] (apparent t, J = 6.8)
6′	38.1 [37.9] (s)	
7′	26.9 [26.7] (t)	H_{ax}, 2.23 [2.18] (m) H_{eq}, 1.62 [1.67] (d, J = 10.2)

[a] Within brackets. [b] See Charts I and II. [c] J in hertz. [d] Overlapping resonances at δ 1.89–1.92.

Chart I. Pyran and Isobutyl Segments of 11e: ^1H and [^{13}C] Resonances



(4) Sawada, T.; Kozuka, M.; Komiya, T.; Amano, T.; Goto, M. *Chem. Pharm. Bull.* **1980**, *28*, 2546. Amano, T.; Komiya, T.; Hori, M.; Goto, M.; Kozuka, M.; Sawada, T. *J. Chromatogr.* **1981**, *208*, 347. Kozuka, M.; Sawada, T.; Kasahara, F.; Mizuta, E.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1952. Kozuka, M.; Sawada, T.; Mizuta, E.; Kasahara, F.; Amano, T.; Komiya, T.; Goto, M. *Ibid.* **1982**, *30*, 1964.

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(8) Baker, R. T.; Smith, H. G. *A Research on the Eucalyptus*; Technical Education Series 24; Technological Museum: New South Wales, 1920; pp 39–40 and 405–409.

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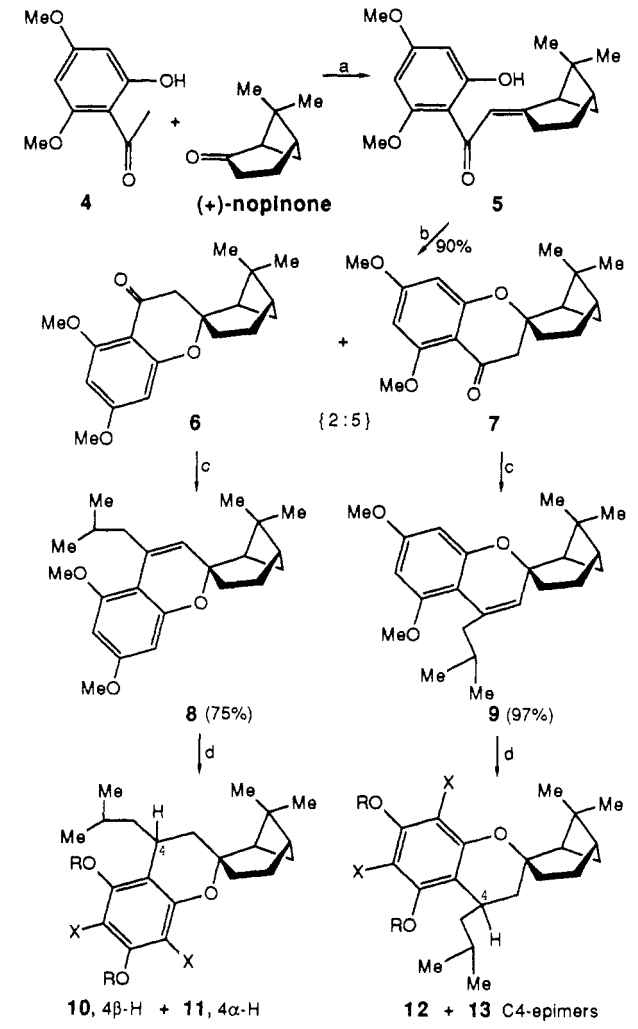
(10) For other examples, see the following. (a) Azadirachtin: Zanno, P. R.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1975**, *97*, 1975. Revised in: Kraus, W.; Bokel, M.; Klenk, A.; Pöhnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435. Broughton, H. B.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1986**, 46. (b) Stoechospermol: Solimabi, L. F.; Kamat, S. Y.; Paknikar, S. K. *Tetrahedron Lett.* **1980**, *21*, 2249. Revised by: Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233. (c) Xylomollin: Kubo, I.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 6704. Revised by: Nakane, M.; Hutchinson, C. R.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 7079. (d) Specionin: Conway, C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605. Revised by: Vander Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719. Van der Eycken, E.; De Bruyen, A.; Van der Eycken, J.; Callant, P.; Vandewalle, M. *Tetrahedron* **1986**, *42*, 5385. (e) **Note added in proof**: Robustadials A and B.[2] Revised by: Cheng, Q.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 4562.

Scheme I[a]



[a] (a) Pyrrolidine/benzene/$-H_2O$; (b) K_2CO_3/90% EtOH/boil; (c) Me_2CHCH_2MgCl, then aqueous HCl; (d) H_2/Pd/C; (e) pyridine–Br_2/CH_2Cl_2; (f) *n*-BuLi/THF, then CO_2, then HCl, then CH_2N_2/Et_2O; (g) DIBAH/toluene; (h) PDC.

remote formyl substituents in **11e** to hydrogen atoms in **11a** does not substantially alter chemical shifts in the nonaromatic segments of these molecules. Although all methine and methylene ^1H resonances for **11e** are severely overlapped,[2] they could be deconvoluted with COSY and HOMO *J*-decoupled spectra.

Assignments of the ^1H and ^{13}C resonances of the pyran positions 3 and 4 and the isobutyl group in **11e** are summarized in Chart I. A COSY spectrum (Figure 2) of **11e** shows the expected correlations between all hydrogens assigned to positions 3–8. The methylene hydrogens at position 3, resolved in HOMO *J*-decoupled spectra (δ 1.75 and 2.19, Figure 3), are coupled with each other (J = 15 Hz) and each with the resonance at δ 2.94 (dddd) whose chemical shift clearly supports assignment to the benzylic hydrogen at position 4. The identical coupling of both C(3) methylene hydrogens (J = 6.9 Hz) with the benzylic C(4) hydrogen agrees with the predictions of the Karplus cor-

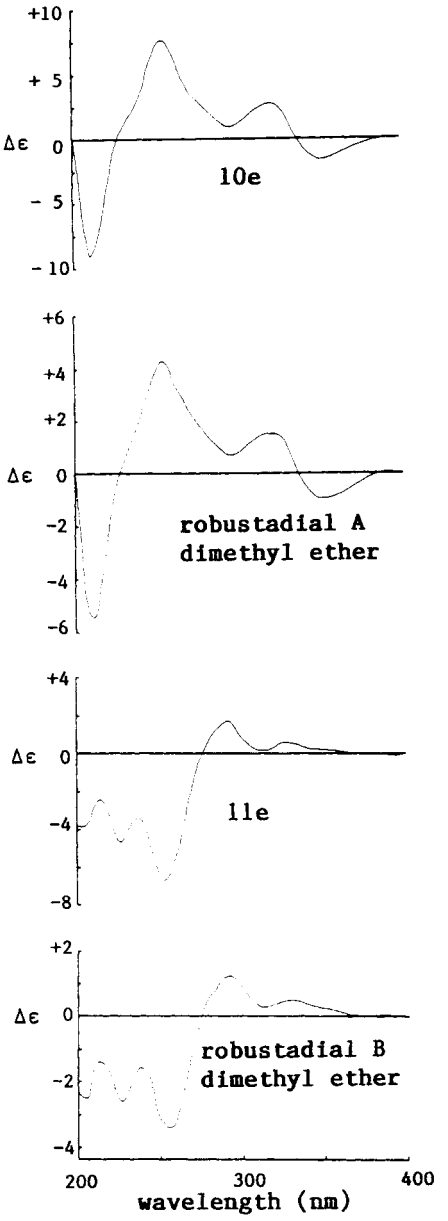
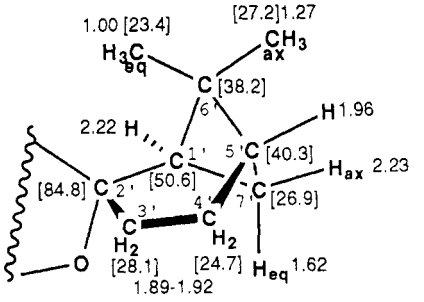


Figure 1. CD spectra of **10e**, **11e**, and robustadial dimethyl ethers.

Chart II. Pinane Segment of 11e: ^1H and [^{13}C] Resonances



relation for vicinal hydrogens with dihedral angles ϕ = 26° and ϕ = 133° for equatorial and axial C(3) hydrogens, respectively. The resonance at δ 2.19 (dd) is assigned to $H(3)_{eq}$ while that at δ 1.75 is assigned to $H(3)_{ax}$ since for geminal hydrogens on a conformationally locked six-membered ring the equatorial hydrogen is typically deshielded relative to the axial hydrogen. Coupling constants for the methylene hydrogens at position 5 and methine hydrogen at position 6 were also readily deduced from the corresponding HOMO *J*-decoupled spectra (Figure 3).

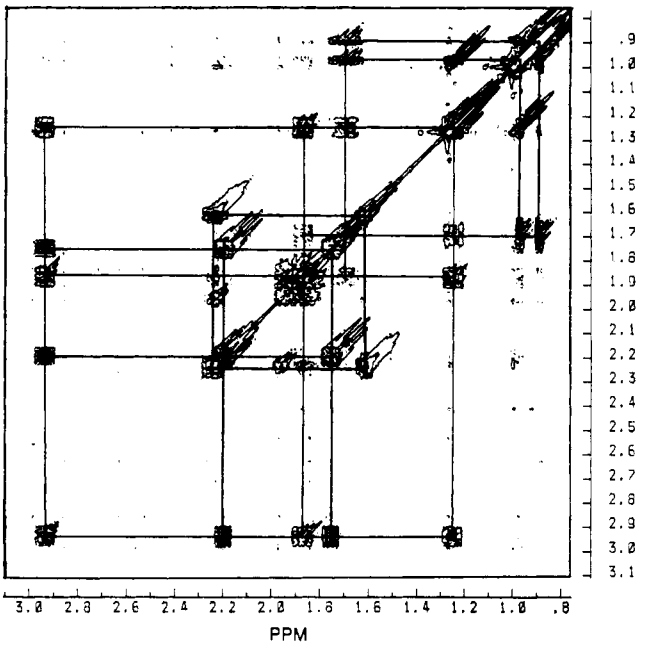
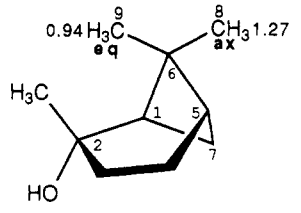


Figure 2. COSY correlations of the hydrogens in **11e**.

Assignments of the ^1H and ^{13}C resonances of the pinane segment of **11e** are summarized in Chart II. The methyl hydrogen singlets for **11e** (in $CDCl_3$) at δ 1.00 and 1.27 are assigned respectively to the equatorial and axial methyls at position 6′ in analogy with the corresponding methyl singlets for 2α-hydroxy-10β-pinane (**14**) which occur at δ 0.94 and 1.27 (in CCl_4).[11] For **11a** these resonances occur



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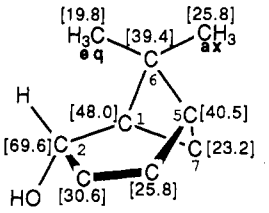

15

at δ 1.03 and 1.30 respectively (in $CDCl_3$). The HETCOR spectrum of **11a** correlates these hydrogen resonances with the methyl carbon resonances at δ 23.5 and 27.3 respectively. By analogy, the carbon resonances in **11e** at δ 23.4 and 27.2 are assigned to the equatorial and axial methyl groups at position 6′ in **11e**. The carbon doublet resonances at δ 40.6 and 50.6 in **11a** are assigned to the bridgehead carbons C(5′) and C(1′) by analogy with the corresponding methine resonances at δ 40.5 and 48.0 in the ^{13}C NMR spectrum of *trans*-nopinol (**15**).[12] Similarly, the carbon doublet resonances at δ 40.3 and 50.6 in **11e** are assigned to C(5′) and C(1′). The C(5′) and C(1′) resonances of **11a** were correlated by HETCOR with the hydrogen resonances at δ 1.93 and 2.20, which are thus bridgehead methine hydrogens at positions 5′ and 1′, respectively. Of the hydrogen resonances in **11e** that might correspond to H(5′), i.e., δ 1.96 or 1.92, the latter clearly shows a large geminal coupling in a HOMO *J*-decoupled spectrum (Figure 4) while the former does not. Therefore, the δ 1.96 resonance is assigned to the methine hydrogen at position 5′. Of the hydrogen resonances in **11e** that might correspond to H(1′), i.e., δ 2.19, 2.22, and 2.23, the first is already assigned to H_{eq} at position 3. The resonances at δ 2.23 is

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(12) Holden, C. M.; Whittaker, D. *Org. Magn. Reson.* **1975**, *7*, 125.

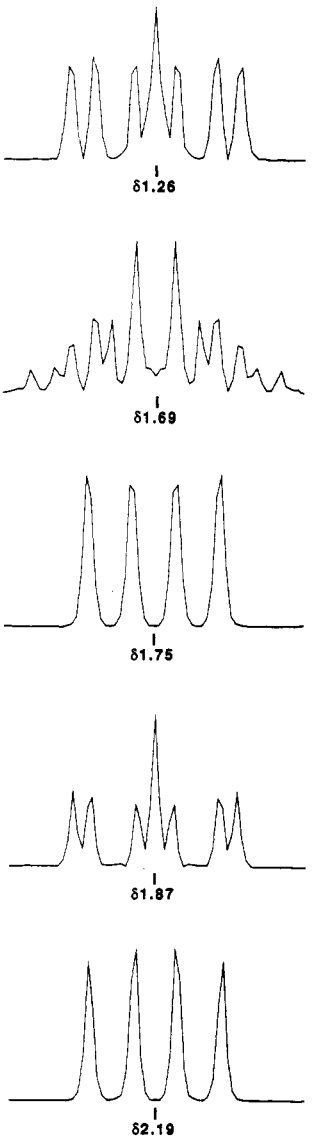


Figure 3. HOMO *J*-decoupled spectra of the pyran and isobutyl hydrogens of **11e**.

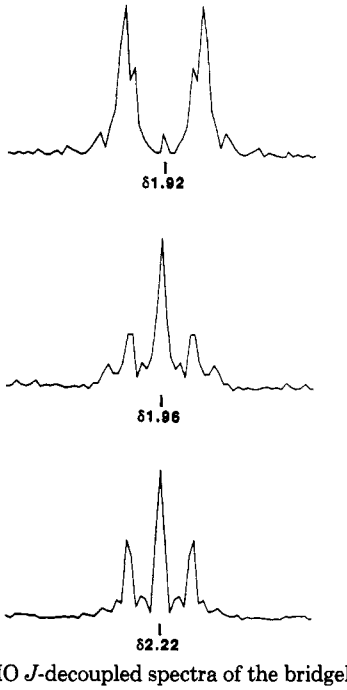


Figure 4. HOMO *J*-decoupled spectra of the bridgehead methine hydrogens of **11e**.

shown below to be a methylene hydrogen. Therefore, the δ 2.22 resonance is assigned to H(1′). Incidentally, the HOMO *J*-decoupled multiplets at δ 1.96 and 2.22 (Figure 4) are remarkably similar for these bridgehead hydrogens at the 5′- and 1′-positions, respectively.

In the ^{13}C NMR spectrum of **15**, the resonances for the quaternary carbons analogous to C(2′) and C(6′) in **11e** appear at δ 69.6 and 39.4, respectively. The nonaromatic singlet carbon resonances in the ^{13}C NMR spectrum of **11e** at δ 84.8 and 38.2 are assigned by analogy to C(2′) and C(6′), respectively.

At δ 1.62 in the ^1H NMR spectrum of **11e**, a doublet appears with J = 10.2 Hz, indicative of geminal coupling. A similar doublet appears at δ 1.40 in the spectrum of β-pinene. The only hydrogen resonances for **11e** remaining unassigned are those of the methylene groups of the pinane moiety. Of these, only H_{eq} at position 7′ is expected to show exclusively geminal coupling owing to vicinal dihedral angles of $\phi = 90°$ with respect to the bridgehead hydrogens[13] at both positions 1′ and 5′. In the COSY spectrum of **11e** (Figure 2), the δ 1.62 resonance is correlated only with that at δ 2.23, which therefore must correspond to H_{ax} at position 7′. The 0.6 ppm downfield shift observed for H_{ax} relative to H_{eq} is well-precedented for methylene hydrogens on puckered cyclobutanes.[14]

Assignment of the ^1H NMR resonances at δ 1.66, 1.67, 2.17, and 2.18 for **11a** is subtle. In the ^1H NMR spectrum of **11e**, the analogous resonances were assigned to methylene hydrogens at positions 3 (δ 1.75 and 2.19) and 7′ (δ 1.62 and 2.23). For **11a**, HETCOR data correlate the resonances at δ 1.67 and 2.18 with the carbon triplet resonance at δ 26.7 while those at δ 1.66 and 2.17 are correlated with the carbon triplet resonance at δ 40.4. In the ^{13}C NMR spectrum of **15**, none of the methylene carbons absorb at lower field than δ 30.6. Therefore, in the ^{13}C NMR spectrum of **11a**, the δ 40.4 resonance is attributed to C(3) and the associated hydrogen resonances (Table I) at δ 1.66 and 2.17 must result from the methylene hydrogens at position 3 in the pyran moiety. It follows that the remaining hydrogen resonances for **11a** at δ 1.67 and 2.18 must correspond with the methylene hydrogens at position 7′ and that the associated carbon resonance (Table I) at δ 26.7 corresponds to C(7′). By analogy, C(3) and C(7′) for **11e** produce resonances at δ 38.9 and 26.9, respectively.

In the carbon spectrum of **11a**, the triplet methylene carbon resonances at δ 27.6 and 24.9 are assigned to C(3′) and C(4′), respectively, by analogy with **15**, for which the corresponding resonances occur at δ 30.6 and 25.8. In the HETCOR spectrum of **11a**, the C(3′) resonance at δ 27.6 is correlated to hydrogen resonances at δ 1.79 and 1.83, identifying them with the methylene hydrogens at position 3′, and the C(4′) resonance at δ 24.9 is correlated with the hydrogen resonances at δ 1.81 and 1.90, identifying them with the methylene hydrogens at position 4′. In the ^1H NMR spectrum of **11e**, the resonances for the methylene hydrogens at positions 3′ and 4′ overlap too intimately at δ 1.89–1.92 to allow further analysis.

Nuclear Overhauser Enhancements for Robustadial B Dimethyl Ethers. NOE data played a major role in the original attempt at structural characterization of robustadial B. All of the major enhancements observed in that study for robustadial B dimethyl ether and their interpretation supporting a bicyclo[3.20]heptyl structure **1b** for the natural product[2] are summarized in Chart III.

Chart III. NOE Data for Robustadial B Dimethyl Ether Interpreted in Terms of Structure 1b

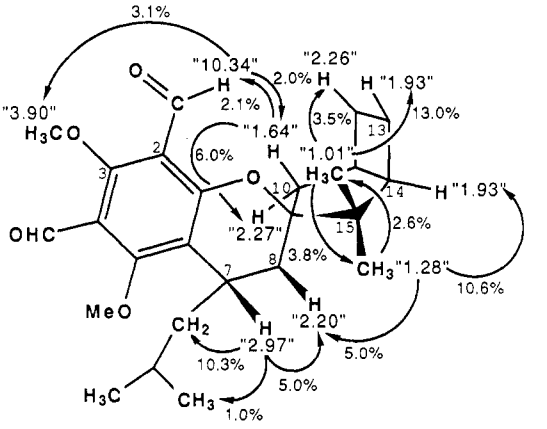
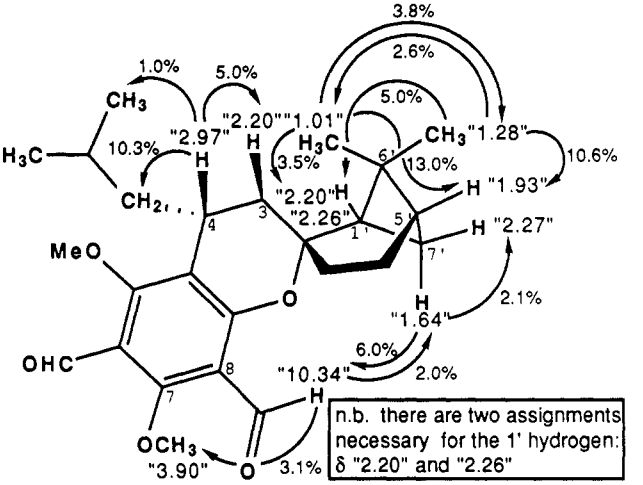


Chart IV. NOE Data for Robustadial B Dimethyl Ether Reinterpreted in Terms of Structure 11e



A reinterpretation of these data in terms of the correct bicyclo[3.1.1]heptyl structure **11e** is summarized in Chart IV. The ^1H NMR chemical shift assignments made in Chart IV agree within ±0.04 ppm with those measured in the present study (see Charts I and II). Instead of the C(15) methyl hydrogens in **1b**, the δ "1.01" and "1.28" resonances are reassigned to the C(6′) methyl hydrogens in **11e**. Instead of the C(10) methylene hydrogens in **1b**, the δ "1.64" and "2.27" resonances are reassigned to the C(7′) methylene hydrogens in **11e**. Whereas a δ "1.93" resonance was previously ascribed to *both the methine hydrogen at C(14) and a methylene hydrogen at C(13)* to explain large NOEs with both C(15) methyl groups in **1b**, this resonance is reassigned to *only the methine hydrogen at C(5′)*, which could reasonably experience large NOEs with both C(6′) methyl groups in **11e**. On the other hand, NOEs previously attributed to two different resonances, i.e., a C(8) *methylene* hydrogen at δ "2.20" and a C(12) *methylene* hydrogen at δ "2.26", were adduced to account for the effects of irradiating one C(15) methyl resonance at δ "1.28" (5.0%) and the other C(15) methyl resonance at δ "1.01" (3.5%). In fact, these NOEs must both be attributed to a single resonance, i.e., that of the C(1′) *methine* hydrogen in **11e**, for which we find a resonance at δ 2.22 (see Chart II). Had HETCOR data been available to associate these enhanced hydrogen resonances with methine rather than methylene carbons, it might have been possible to decide between interpretation of the data as supporting **1b** or **11e**.[10e] Nevertheless, the distinction between enhancements at δ 2.26, 2.22, or 2.20 is fraught

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with uncertainty. Thus, the NMR data obtained in the original study were consistent with both structures **1b** and **11e**. A choice in favor of structure **11e** might have been made on the basis of the similarity between the chemical shifts of the ^{13}C NMR resonances at δ 40.5 and 51.0 previously attributed to the bridgehead methine carbons at positions 11 and 14 in **1b** and the known chemical shifts, i.e., δ 40.5 and 48.0, for the bridgehead methine carbons in **15**.[12] We conclude that all possible isomeric structures must be systematically considered to avoid misinterpretation of non-X-ray data for characterizing complex organic molecules. It should be mandatory that all isomeric possibilities are explicitly excluded before it can be claimed that "structures have been determined".

Experimental Section

General. Many general procedures were described previously.[3b] (+)-Nopinone was prepared by the method of Konopelski and Djerassi[15] $[\alpha]^{20} = +33.5°$ (*c* 1.64, methanol) (lit.[15] $[\alpha]^{20} = +36.6°$ (*c* 1.6, methanol)). Pyridine perbromide was prepared by the method of McElvain and Morris.[10] On storage it turns into a black powder, so it was prepared fresh whenever required. All chromatography solvents were distilled prior to use. The term "reduced pressure" refers to solvent removal via a Büchi Rotavapor under water-aspirator reduced pressure, followed by evacuation of the flask through a dry ice cooled trap at 0.2 mm for several hours. Flash chromatography[16] was performed on ~40 μm average particle size silica gel supplied by J. T. Baker Chemical Co. Melting points were obtained in open capillary tubes and are uncorrected. The purity of all titled compounds was estimated to be at least 95% by TLC and ^1H NMR analysis.

^1H NMR spectra were recorded at 200 MHz in $CDCl_3$. Higher field NMR spectra were measured at 400.13 MHz for ^1H and 100.627 for ^{13}C. Proton spectra, COSY, and *J*-resolved experiments were run in a 5-mm proton probe head. HETCOR experiments were run in a 10-mm broad band probe head. The 2D spectra were acquired with quadrature detection in the f_2 dimension, sine-bell multiplication in f_1 and f_2, and zero-filling in f_1. Specific parameters follow: ^1H–^1H COSY sequence, Δ–90°–t_1–90°–t_2, Δ = 4.0 s, 90° pulse = 8 μs, acquisition time (t_2) = 0.772 s, 512 increments, spectral width in f_1 and f_2 = 1326.26 Hz, size = 2K, digital resolution = 1.295 Hz/point (in both domains), 16 transients, phase cycling = 4 transients; ^1H–^1H 2D-*J*-resolved sequence, Δ–90°–t_1–180°–t_1–t_2, Δ = 10 s, 90° pulse = 26.5 μs, 180° pulse = 53 μs, acquisition time (t_2) = 1.278 s, 32 increments, spectral width in f_1 and f_2 = 50.1 and 1602.56 Hz, respectively, size = 4K, digital resolution = 0.783 Hz/point (in both domains), 64 transients, phase cycling = 4 transients; ^1H–^{13}C heteronuclear shift correlated spectrum sequence, Δ–90°(^1H)–t_1/2180°(^{13}C)–t_1/2–Δ_1–90°(^1H,^{13}C)–Δ_2–t_2, Δ = 4 s, 90° pulse on carbon = 15 μs, 180° pulse on carbon = 30 μs, 90° pulse on hydrogen = 47.5 μs, Δ_1 = 4 ms, Δ_2 = 2.4 ms, acquisition time (t_2) = 0.508 s, size = 2K, 512 increments, spectral widths in f_1 = 2016.13 and 726 Hz, spectral widths in f_2 each = 660.5 Hz, digital resolution = 1.969 Hz/point in domain 2 and 1.29 Hz/point in domain 1, 32 transients, phase cycling = 8 transients.

Chromanones 6 and 7. 2-Hydroxy-4,6-dimethoxyacetophenone (**4**, 7.73 g, 39.4 mmol), (+)-nopinone (5.56 g, 40.3 mmol), and pyrrolidine (1.43 g, 20.1 mmol) in benzene (16 mL) were allowed to stand at room temperature for 37.5 h and were then heated at reflux for 24 h.[17] Water was removed via a Dean–Stark trap. After cooling, the reaction mixture was poured into a 1% aqueous HCl solution (150 mL). This was extracted with methylene chloride (3 × 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield 12.00 g of an oil. This was chromatographed on a Waters Prep LC System-500A with one silica gel cartridge using 20% ethyl acetate in hexanes. Three fractions were collected. The first fraction contained enone **5** (1.74 g) while the second fraction contained **4** and **5**. Solvent removal from the second fraction under reduced pressure afforded a residue, which solidified on standing overnight. This was triturated with hexanes until only colorless **4** (2.34 g) remained. The combined hexane washes were concentrated under reduced pressure, and the residue thus obtained was flash chromatographed (80-mm-diameter silica gel column using 5% ethyl acetate in hexanes) to yield enone **5** (663 mg, 40.7%) and acetophenone **4** (1.72 g). The third fraction from the "Prep-500" contained **6** and **7**. These isomers were separated by flash chromatography, providing **6** (272 mg, 4.6%) and **7** (921 mg, 15.6%) with 47.5% conversion of **4**. Enone **5** was cyclized to provide chromanones **6** and **7**. A mixture of **5** (1.80 g, 5.7 mmol) and anhydrous K_2CO_3 (2.5 g) in ethanol (90%, 50 mL) was heated under reflux for 12 h. After cooling, the top layer was separated, and the lower layer was extracted with ethyl acetate (40 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Chromatography of the residue on a Waters Prep LC System/500A with one silica gel cartridge using 20% ethyl acetate in hexanes provided **5** (222 mg, 12.3%), **6** (0.443 g, 28.0%), and **7** (0.982 g, 62.0%). Enone **5**: ^1H NMR δ 0.76 (s, 3 H), 1.28 (s, 3 H), 1.21–1.61 (m, 2 H), 1.79–2.14 (m, 3 H), 2.21–2.62 (m, 2 H), 2.71–2.96 (m, H), 3.13–3.34 (m, H), 3.78 (s, 3 H), 3.79 (s, 3 H), 5.88 (d, J = 2.3 Hz, H), 6.05 (d, J = 2.3 Hz, H), 6.77 (br s, H); ^{13}C NMR δ 22.17 (–, q), 23.94 (+, t), 24.06 (+, t), 26.15 (–, q), 27.24 (+, t), 40.45 (–, d), 41.16 (+, s), 54.61 (–, d), 55.39 (–, q), 55.52 (–, q), 90.86 (–, d), 93.65 (–, d), 106.87 (+, s), 123.08 (–, d), 161.83 (+, s), 165.16 (+, s), 167.53 (+, s), 168.01 (+, s), 194.20 (+, s); HRMS calcd for $C_{19}H_{24}O_4$ 316.1668, found 316.1666. Chromanone **6**: ^1H NMR δ 0.95 (s, 3 H), 1.21 (s, 3 H), 1.49–1.63 (m, H), 1.75–2.34 (m, 7 H), 2.73 (d, J = 16.1 Hz, H), 2.82 (d, J = 16.1 Hz, H), 3.79 (s, 3 H), 3.84 (s, 3 H), 5.98 (s, 2 H); ^{13}C NMR δ 23.04 (–, q), 24.36 (+, t), 26.39 (+, t), 27.17 (–, q), 28.41 (+, t), 37.85 (+, s), 40.19 (–, d), 48.56 (–, d), 50.74 (+, t), 55.31 (–, q), 55.83 (–, q), 85.47 (+, s), 92.02 (–, d), 93.88 (–, d), 105.57 (+, s), 161.49 (+, s), 163.32 (+, s), 165.78 (+, s), 190.03 (+, s); HRMS calcd for $C_{19}H_{24}O_4$ 316.1668, found 316.1672. Chromanone **7**: ^1H NMR δ 1.00 (H, m), 1.08 (s, 3 H), 1.14 (s, 3 H), 1.68–2.34 (7 H), 2.66 (m, 2 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 5.92 (d, J = 2.3 Hz, H), 5.95 (d, J = 2.2 Hz, H); ^{13}C NMR δ 22.92 (–, q), 23.59 (+, t), 26.46 (+, t), 27.04 (–, q), 28.11 (+, t), 38.11 (+, s), 40.39 (–, d), 47.91 (–, d), 49.73 (+, t), 55.25 (–, q), 55.74 (–, q), 85.90 (+, s), 91.87 (–, d), 93.76 (–, d), 105.54 (+, s), 161.56 (+, s), 163.02 (+, s), 165.73 (+, s), 190.07 (+, s); HRMS calcd for $C_{19}H_{24}O_4$ 316.1668, found 316.1677.

Isomerization of 6 to 7. Chromanone **6** (115 mg, 0.37 mmol) and anhydrous potassium carbonate (2.5 g) in 10% aqueous ethanol (50 mL) were heated at reflux under nitrogen. Aliquots (2–3 mL) were removed and diluted with methylene chloride (20 mL), dried ($MgSO_4$), and stripped of volatiles under reduced pressure to provide samples for subsequent ^1H NMR analysis. The following isomeric ratios were determined by integration of the pairs of doublet resonances attributed to the methylene hydrogens α to the carbonyl in the region 480–600 Hz: 1.0 h (62:38), 7.5 h (29:71), 22.5 h (28:72), 48 h (23:77), 119 h (22:77).

Isomerization of 7 to 6. Chromanone **7** (108 mg, 0.35 mmol) and anhydrous potassium carbonate (2.5 g) in 10% aqueous ethanol (50 mL) were heated at reflux under nitrogen. Aliquots (2–3 mL) were removed and analyzed as above: 0.5 h (14:86), 1.5 h (17:83), 8.0 h (25:75), 77 h (25:75).

Alkene 8. Ketone **6** (1.30 g, 4.1 mmol) was treated with isobutylmagnesium chloride by following a procedure described earlier for the camphane analogue.[5] The crude product thus obtained (1.57 g) was dissolved in methylene chloride (25 mL), stirred with 10% aqueous HCl (10 mL) at room temperature for 18 h, and worked up in the usual manner. The crude dehydration product was flash chromatographed (2% ethyl acetate in hexanes) to yield **8** (1.10 g, 75.3%): ^1H NMR δ 0.76 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.94 (s, 3 H), 1.15 (s, 3 H), 1.48–2.28 (m, 10 H), 2.56–2.73 (m, H), 3.74 (s, 6 H), 5.33 (s, H), 5.99 (d, J = 2.5 Hz, H), 6.05 (d, J = 2.4 Hz, H); ^{13}C NMR δ 21.90 (–, q), 22.94 (–, q), 23.42 (–, q), 24.46 (+, t), 25.55 (+, t), 26.96 (–, d), 27.23 (–, q), 30.64 (+, t), 37.78 (+, s), 40.50 (–, d), 44.64 (+, s), 48.93 (–, d), 55.06 (–, q), 55.20 (–, q), 81.45 (+, s), 92.04 (–, d), 94.72 (–,

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d), 106.32 (+, s), 128.32 (−, d), 131.28 (+, s), 155.98 (+, s), 157.44 (+, s), 160.32 (+, s); HRMS calcd for $C_{23}H_{32}O_3$ 356.2351, found 356.2351.

Chromans 10a and 11a. 2*H*-Chromene **8** was hydrogenated over 5% palladium on charcoal as described earlier for the camphane analogue.[5] The crude product was chromatographed by reverse-phase HPLC (20% water in acetonitrile at 12 mL/min) to give unreacted **8** after 96 min (6.3%), **10a** after 104 min (10.7% based on **8** consumed), and **11a** after 110 min (85.9% based on **8** consumed). Chroman **10a**: ^{1}H NMR δ 0.86 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H), 0.96 (s, 3 H), 1.17 (s, 3 H), 1.05–1.33 (m, H), 1.45–2.25 (m, 12 H), 2.81 (m, H), 3.71 (s, 3 H), 3.73 (s, 3 H), 5.94 (d, J = 2.4 Hz, H), 5.99 (d, J = 2.5 Hz, H); ^{13}C NMR δ 21.29 (−, q), 23.30 (−, q), 24.14 (−, q), 24.98 (+, t), 25.63 (−, d), 26.37 (+, t), 27.01 (−, d), 27.75 (−, q), 31.12 (+, t), 37.85 (+, s), 40.68 (−, d), 40.78 (+, t), 44.20 (+, t), 47.22 (−, d), 55.06 (−, q), 55.15 (−, q), 81.52 (+, s), 91.62 (−, d), 94.51 (−, d), 108.94 (+, s), 155.55 (+, s), 158.66 (+, s), 159.00 (+, s); HRMS calcd for $C_{23}H_{34}O_3$ 358.2508, found 358.2520. Chroman **11a**: ^{1}H NMR δ 0.88 (d, J = 6.4 Hz, 3 H), 0.95 (d, J = 6.3, 3 H), 1.00 (s, 3 H), 1.20 (m, H), 1.25 (s, 3 H), 1.50–1.98 (m, 9 H), 2.03–2.27 (m, 3 H), 2.83 (m, H), 3.72 (s, 3 H), 3.74 (s, 3 H), 5.97 (d, J = 2.4 Hz, H), 6.00 (d, J = 2.4 Hz, H); ^{13}C NMR δ 21.34 (−, q), 23.50 (−, q), 24.06 (−, q), 24.93 (+, t), 25.98 (−, d), 26.65 (−, d), 26.74 (+, t), 27.31 (−, q), 27.58 (+, t), 37.94 (+, s), 40.43 (+, t), 40.55 (−, d), 44.21 (+, t), 50.55 (−, d), 54.96 (−, q), 55.09 (−, q), 81.01 (+, s), 91.54 (−, d), 94.54 (−, d), 108.94 (+, s), 155.21 (+, s), 158.91 (+, s), 159.05 (+, s); HRMS calcd for $C_{23}H_{34}O_3$ 358.2508, found 358.2520.

Alkene 9. Ketone **7** was treated with isobutylmagnesium chloride as described above for ketone **6**. The crude product was taken into methylene chloride, stirred with 10% aqueous HCl at room temperature for 6 h, and then worked up in the usual manner. The crude product was flash chromatographed through silica gel (2% ethyl acetate in hexanes) to provide **9** (97.%): ^{1}H NMR δ 0.77 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H), 1.11 (s, 3 H), 1.16 (s, 3 H), 1.75–2.35 (m, 10 H), 2.55 (m, H), 3.74 (s, 3 H), 3.75 (s, 3 H), 5.33 (s, H, 6.00 (d, J = 2.4 Hz, H), 6.04 (d, J = 2.4 Hz, H).

Chromans 12a and 13a. 2*H*-Chromene **9** was hydrogenated as for **8** above. The crude product was chromatographed by HPLC using a Whatman Partisil M20 column (1% ethyl acetate in hexanes at 9 mL/min) to give, after 54 min, a mixture of chromans **12a** and **13a** (1.12 g). This was separated by reverse-phase HPLC using a Whatman Partisil 10 ODS-3 column (20% water in acetonitrile at 12 mL/min) to give **12a** after 114 min (160 mg, 11.4%) and **13a** after 118 min (926 mg, 65.8%). Chroman **12a**: ^{1}H NMR δ 0.85 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.97–2.27 (m, 7 H), 1.04 (s, 3 H), 1.06 (s, 3 H), 1.07 (s, 3 H), 2.75 (m, H), 3.71 (s, 3 H), 3.73 (s, 3 H), 5.92 (d, J = 2.4 Hz, H), 5.98 (d, J = 2.4 Hz, H); ^{13}C NMR δ 21.24 (−, q), 23.16 (−, q), 24.24 (+, t), 24.27 (−, q), 25.63 (−, d), 27.00 (+, t), 27.04 (−, d), 27.50 (−, q), 31.11 (+, t), 38.25 (+, s), 40.32 (+, t), 41.26 (−, d), 44.55 (+, t), 46.00 (−, d), 55.02 (−, q), 55.19 (−, q), 82.00 (+, s), 91.50 (−, d), 94.43 (−, d), 108.73 (+, s), 155.36 (+, s), 158.86 (+, s), 158.97 (+, s); HRMS calcd for $C_{23}H_{34}O_3$ 358.2508, found 358.2509. Chroman **13a**: ^{1}H NMR δ 0.84 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 1.00–1.18 (m, 2 H), 1.13 (s, 3 H), 1.23 (s, 3 H), 1.35–1.55 (m, H), 1.55–2.00 (7 H), 2.02–2.35 (m, 3 H), 2.85 (m, H), 3.72 (s, 3 H), 3.74 (s, 3 H), 5.94 (d, J = 2.4 Hz, H), 6.01 (d, J = 2.4 Hz, H); ^{13}C NMR δ 21.38 (−, q), 23.49 (−, q), 24.18 (+, t), 24.21 (−, q), 25.86 (−, d), 26.45 (+, t), 26.48 (−, d), 27.20 (+, t), 27.51 (−, q), 38.53 (+, s), 40.88 (−, d), 40.96 (+, t), 44.52 (+, t), 51.08 (−, d), 54.96 (−, q), 55.11 (−, q), 81.65 (+, s), 91.56 (−, d), 94.76 (−, d), 109.15 (+, s), 155.18 (+, s), 159.01 (+, s), 159.06 (+, s); HRMS calcd for $C_{23}H_{34}O_3$ 358.2508, found 358.2504.

Dibromide 10b. Freshly prepared pyridine perbromide[18] (230 mg, 0.96 mmol) was added in portions (~20 mg each), with stirring to a solution of chroman **10a** (170 mg, 0.47 mmol) in CH_2Cl_2 (10 mL) over 10 min. The resulting pale yellow solution was stirred for 5 min, then diluted with ether (25 mL), washed with water (3 × 2 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (2% ethyl acetate in hexanes) and crystallization from hexanes to give **10b** (235 mg, 96%): mp 127–9 °C; ^{1}H NMR δ 0.88 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.95 (s, 3 H), 1.18 (s, 3 H), 1.28 (m, H), 1.52–2.34 (12 H), 2.95 (m, H), 3.74 (s, 3 H), 3.81 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}BrO_3$ 516.0700, found 516.0677; MS, m/z (relative intensity) 518 (1.0), 516 (2.3, M^+), 473 (3.8), 461 (23.9), 459 (44.8), 327 (48.6), 325 (100), 191 (28.8), 135 (12.0), 121 (14.6), 93 (17.6), 91 (15.5), 69 (40.5), 55 (11.9).

Diester 10c. Dibromide **13b** was lithiated with *n*-butyllithium, carboxylated, and esterified as described previously for the camphane analogue[5] to give diester **10c** (82%) after flash chromatography (10% ethyl acetate in hexanes): ^{1}H NMR δ 0.87 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.93 (s, 3 H), 1.17 (s, 3 H), 1.25 (m, H), 1.44 (m, H), 1.57–2.25 (11 H), 2.87 (m, H), 3.73 (s, 3 H), 3.76 (s, 3 H), 3.84 (s, 3 H), 3.86 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2604; MS, m/z (relative intensity) 474 (1.5, M^+), 443 (8.6), 417 (28.6), 385 (100), 339 (15.0), 307 (73.6), 283 (21.8), 251 (74.5), 191 (27.1), 93 (12.9), 91 (10.1), 81 (32.8), 69 (77.7), 55 (25.1).

Diol 10d. Diester **10c** was reduced with diisobutylaluminum hydride (DIBAH) as described earlier for the camphane analogue.[5] The crude product was purified by flash chromatography (30% ethyl acetate in hexanes) to give diol **10d** (97%): ^{1}H NMR δ 0.89 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.97 (s, 3 H), 1.18 (s, 3 H), 1.25 (m, H), 1.47–2.57 (14 H), 2.90 (m, H), 3.72 (s, 3 H), 3.82 (s, 3 H), 4.61 and 4.64 (2 s, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2708; MS, m/z (relative intensity) 418 (1.1, M^+), 400 (2.7), 361 (9.5), 343 (45.7), 265 (52.4), 249 (9.0), 209 (38.2), 191 (19.4), 149 (8.0), 119 (14.2), 95 (14.1), 83 (15.7), 81 (42.4), 69 (100), 55 (30.3).

Dialdehyde 10e. A mixture of diol **10d** (110 mg, 0.26 mmol) and pyridinium dichromate (2.0 g, 5.32 mmol) in CH_2Cl_2 (8 mL) was stirred at room temperature for 24 h, then diluted with ether (20 mL), and worked up as described earlier.[5] The crude product was purified by flash chromatography (15% ethyl acetate in hexanes) to give dialdehyde **10e** (95 mg, 87%): UV (methanol) λ_{max} 262 (ϵ 25 100), 282 (17 900), 326 nm (5100); CD (methanol) 212 ($\Delta\epsilon$ −9.04), 256 (+7.41), 275 (+3.01), 320 (+2.64), 354 nm (−1.63); $[\alpha]^{20}$ = +49.0° (c 3.5, methanol); ^{1}H NMR δ 0.89 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.97 (s, 3 H), 1.20 (s, 3 H), 1.27 (m, H), 1.49–2.36 (12 H), 2.96 (m, H), 3.82 (s, 3 H), 3.90 (s, 3 H), 10.24 (s, H), 10.33 (s, H); ^{1}H NMR (pyridine-d_5) 0.91 (d, J = 6.8 Hz, 3 H), 0.92 (s, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.12 (s, 3 H), 1.28 (m, H), 1.47–2.38 (12 H), 3.09 (m, H), 3.86 (s, 3 H), 3.99 (s, 3 H), 10.51 (s, H), 10.65 (s, H); ^{13}C NMR δ 20.90 (−, q), 23.27 (−, q), 23.87 (−, q), 24.69 (+, t), 25.40 (−, d), 26.50 (+, t), 26.98 (−, d), 27.55 (−, q), 30.82 (+, t), 38.07 (+, s), 39.21 (+, t), 40.36 (−, d), 43.93 (+, t), 48.86 (−, d), 62.40 (−, q), 64.84 (−, q), 85.65 (+, s), 115.31 (+, s), 116.19 (+, s), 118.83 (+, s), 163.64 (+, s), 165.03 (+, s), 165.50 (+, s), 187.77 (−, d, 2 C); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2395; MS, m/z (relative intensity) 414 (0.3, M^+), 399 (1.9), 371 (2.6), 357 (38.8), 279 (17.4), 223 (100), 191 (8.0), 121 (8.1), 105 (10.6), 91 (23.5), 81 (10.6), 69 (32.3), 55 (15.7).

Dibromide 11b was prepared and purified by following the procedure described above for **10b**. Crystallization from hexanes delivered **11b** (99%): mp 85–6 °C; ^{1}H NMR δ 0.88 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.98 (s, 3 H), 1.25 (m, H), 1.26 (s, 3 H), 1.47–2.06 (9 H), 2.13–2.33 (3 H), 2.96 (m, H), 3.75 (s, 3 H), 3.82 (s, 3 H); HMRS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0733; MS, m/z (relative intensity) 518 (0.9), 516 (1.2, M^+), 459 (24.1), 325 (52.6), 191 (9.3), 135 (10.8), 121 (14.0), 95 (15.8), 93 (15.1), 69 (100).

Diester 11c was obtained and purified by following the procedure described above for **10c**. Crystallization from ethyl acetate/hexanes delivered **11c** (63%): mp 154 °C; ^{1}H NMR δ 0.87 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.96 (s, 3 H), 1.19 (m, H), 1.24 (s, 3 H), 1.48–2.04 (9 H), 2.06–2.27 (3 H), 2.92 (m, H), 3.74 (s, 3 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 3.87 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2592; MS, m/z (relative intensity) 474 (1.0, M^+), 443 (8.0), 417 (26.9), 399 (11.2), 385 (100), 339 (17.6), 307 (78.4), 283 (24.8), 251 (74.4), 191 (15.8), 97 (22.9), 93 (14.4), 83 (31.9), 69 (87.9), 55 (50.5).

Diol 11d was prepared in 93% yield by following the procedure described above for **10d**: ^{1}H NMR δ 0.88 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 1.21 (m, H), 1.27 (s, 3 H), 1.49–2.57 (14 H), 2.95 (m, H), 3.74 (s, 3 H), 3.82 (s, 3 H), 4.64 (br

(18) McElvain, S. M.; Morris, L. R. *J. Am. Chem. Soc.* **1951**, *73*, 206.

s, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2692; MS, m/z (relative intensity) 418 (1.1, M^+), 400 (3.3), 361 (9.1), 343 (60.6), 325 (10.6), 283 (15.5), 265 (64.7), 249 (11.2), 209 (46.2), 193 (7.1), 191 (12.1), 95 (18.8), 81 (44.5), 69 (100), 55 (44.4).

Dialdehyde 11e was prepared and purified by following the procedure described above for dialdehyde **10e**: yield 88%; UV (methanol) λ_{max} 262 (ϵ 25 500), 282 (16 400), 326 nm (4200); CD (methanol) 227 ($\Delta\epsilon$ -4.63), 255 (-6.58), 292 (+1.69), 330 (+0.52), 354 nm (+0.17); $[\alpha]^{20}$ = -67.8° (*c* 1.43, methanol); ^{1}H NMR δ 0.88 (d, J = 6.4 Hz, 3 H), 0.96 (d, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 1.25 (s, 3 H), 1.28 (m, H), 1.49–2.09 (9 H), 2.13–2.37 (3 H), 2.95 (m, H), 3.82 (s, 3 H), 3.90 (s, 3 H), 10.24 (s, H), 10.33 (s, H); ^{13}C NMR 20.90 (-, q), 23.39 (-, q), 23.84 (-, q), 24.71 (+, t), 25.62 (-, d), 26.65 (-, d), 26.86 (+, t), 27.16 (-, q), 28.11 (+, t), 38.07 (+, s), 38.92 (+, t), 40.32 (-, d), 44.30 (+, t), 50.65 (-, d), 62.43 (-, q), 64.84 (-, q), 84.79 (+, s), 115.59 (+, s), 115.99 (+, s), 118.62 (+, s), 163.38 (+, s), 165.60 (+, s), 165.68 (+, s), 187.68 (-, d), 187.77 (-, d); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2433; MS, m/z (relative intensity) 414 (0.5, M^+), 399 (1.3), 371 (2.3), 357 (26.1), 279 (19.3), 263 (5.1), 223 (100), 149 (36.7), 136 (2.1), 121 (8.9), 105 (9.6), 91 (22.6), 69 (40.7), 55 (29.7).

Dibromide 12b was prepared by following the procedure described above for dibromide **10b**. Crystallization from hexanes delivered **12b** (98%): mp 133–4 °C; ^{1}H NMR δ 0.87 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 1.10 (s, 3 H), 1.17 (s, 3 H), 1.19 (m, 2 H), 1.51–2.40 (11 H), 2.90 (m, H), 3.74 (s, 3 H), 3.82 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0697; MS, m/z (relative intensity) 518 (1.8), 516 (3.9, M^+), 459 (8.9), 325 (16.0), 191 (5.2), 137 (10.3), 121 (8.6), 95 (14.9), 81 (42.8), 69 (100), 57 (25.3), 55 (22.9).

Diester 12c was prepared and purified by following the procedure described above for diester **10c**. Crystallization from hexanes delivered **12c** (76%): mp 82–4 °C; ^{1}H NMR 0.86 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.95 (s, 3 H), 1.04 (m, H), 1.10 (s, 3 H), 1.22 (m, H), 1.52–2.35 (11 H), 2.80 (m, H), 3.73 (s, 3 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 3.87 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2634; MS, m/z (relative intensity) 474 (1.9, M^+), 443 (8.5), 417 (32.5), 399 (11.1), 385 (100), 339 (16.2), 307 (65.8), 283 (19.2), 251 (66.6), 191 (19.6), 93 (6.3), 69 (15.7), 55 (10.6).

Diol 12d was prepared by following the procedure described for diol **10d**: yield, 99%; ^{1}H NMR δ 0.87 (d, J = 6.4 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 1.11 (s, 6 H), 1.17 (m, 2 H), 1.49–2.62 (13 H), 2.84 (m, H), 3.72 (s, 3 H), 3.82 (s, 3 H), 4.64 (br s, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2715; MS, m/z (relative intensity) 418 (0.6, M^+), 361 (2.3), 343 (12.2), 265 (10.1), 209 (9.3), 191 (5.6), 137 (7.7), 95 (12.4), 83 (13.7), 81 (39.9), 69 (100), 57 (36.6), 55 (33.4).

Dialdehyde 12e was prepared and purified by following the procedure described above for dialdehyde **10e**: yield, 87%; UV (methanol) λ_{max} 262 (ϵ 20 700), 282 (14 450), nm 326 (3850); CD (methanol) 213 ($\Delta\epsilon$ +3.63), 231 (-2.42), 253 (-4.19), 291 (-0.42), nm 323 (-1.77); $[\alpha]^{20}$ = -69.3° (*c* 3.57, methanol); ^{1}H NMR δ 0.87 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.98 (s, 3 H), 1.07 (s, 3 H), 1.14 (m, 2 H), 1.52–2.43 (11 H), 2.85 (m, H), 3.82 (s, 3 H), 3.89 (s, 3 H), 10.25 (s, H), 10.34 (s, H); ^{13}C NMR δ 20.77 (-, q), 23.67 (-, q), 24.04 (+, t), 24.07 (-, q), 25.39 (-, d), 27.03 (-, d), 27.34 (-, q), 27.49 (+, t), 30.87 (+, t), 37.95 (+, s), 38.98 (+, t), 40.98 (-, d), 44.37 (+, t), 46.74 (-, d), 62.32 (-, q), 64.70 (-, q), 85.27 (+, s), 115.23 (+, s), 116.11 (+, s), 118.08 (+, s), 163.38 (+, s), 165.32 (+, s), 165.52 (+, s), 187.84 (-, d), 188.20 (-, d); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2406; MS, m/z (relative intensity) 414 (0.6, M^+), 371 (3.3), 357 (37.1), 301 (4.8), 279 (18.7), 223 (100), 191 (8.4), 121 (6.5), 105 (4.9), 91 (8.1), 69 (21.5), 55 (7.1).

Dibromide 13b was prepared by following the procedure described above for dibromide **10b**. Crystallization from hexanes delivered **13b** (100%): mp 154–5 °C; ^{1}H NMR δ 0.86 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H) 1.16 (m, 2 H), 1.24 (s, 3 H), 1.25 (s, 3 H), 1.44 (m, H), 1.57–2.43 (10 H), 3.00 (m, H), 3.75 (s, 3 H), 3.82 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0714; MS, m/z (relative intensity) 518 (3.5), 516 (8.4, M^+), 459 (70.5), 457 (35.3), 379 (12.7), 325 (100), 244 (8.2), 191 (18.9), 147 (7.6), 121 (17.1), 91 (14.3), 69 (27.7).

Diester 13c was prepared and purified by following the procedure described above for diester **10c**: yield, 85%; ^{1}H NMR δ 0.85 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.97 (s, 3 H), 1.13 (m, 2 H), 1.21 (s, 3 H), 1.40 (m, H), 1.54–2.40 (10 H), 2.94 (m, H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 3.87 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2597; MS, m/z (relative intensity) 474 (2.0, M^+), 443 (7.9), 417 (33.1), 385 (100), 339 (11.7), 307 (56.1), 283 (17.3), 251 (64.0), 191 (16.0), 91 (5.9), 69 (13.0), 55 (8.2).

Diol 13d was prepared by following the procedure described for diol **10d**: yield, 98%; ^{1}H NMR δ 0.86 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 1.19 (s, 3 H), 1.23 (m, 2 H), 1.27 (s, 3 H), 1.44–2.58 (13 H), 2.99 (m, H), 3.74 (s, 3 H), 3.82 (s, 3 H), 4.64 and 4.65 (2 br s, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2717; MS, m/z (relative intensity) 418 (4.7, M^+), 400 (4.1), 343 (100), 325 (11.6), 283 (15.0), 265 (69.8), 249 (12.4), 209 (57.6), 191 (16.4), 118 (8.3), 93 (10.0), 91 (14.0), 83 (31.7), 81 (8.1), 69 (24.0), 55 (12.9).

Dialdehyde 13e was prepared and purified by following the procedure described above for dialdehyde **10e**: yield, 87%; UV (methanol λ_{max} 262 (ϵ 20 750), 282 (14 400), 326 nm (4000); CD (methanol) 214 ($\Delta\epsilon$ -3.22), 236 (+1.93), 251 (+4.51), 290 (-1.16), 351 nm (-0.58); $[\alpha]^{20}$ = +53.8° (*c* 4.37, methanol); ^{1}H NMR δ 0.85 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 1.05 (s, 3 H), 1.16 (m, 2 H), 1.23 (s, 3 H), 1.46–2.06 (8 H), 2.11–2.46 (3 H), 2.96 (m, H), 3.82 (s, 3 H), 3.89 (s, 3 H), 10.25 (s, H), 10.33 (s, H); ^{13}C NMR δ 20.95 (-, q), 23.98 (-, q), 24.05 (+, t), 24.14 (-, q), 25.65 (-, d), 26.50 (-, d), 27.33 (-, q), 27.39 (+, t), 27.65 (+, t), 38.21 (+, s), 39.23 (+, t), 40.46 (-, d), 44.50 (+, t), 51.19 (-, d), 62.41 (-, q), 64.73 (-, q), 85.02 (+, s), 115.81 (+, s), 116.16 (+, s), 118.68 (+, s), 163.42 (+, s), 165.14 (+, s), 165.67 (+, s), 187.81 (-, d), 188.40 (-, d); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2399; MS, m/z (relative intensity) 414 (1.1, M^+), 399 (2.8), 371 (4.1), 357 (52.7), 301 (5.1), 279 (23.4),224 (13.5), 223 (100), 191 (7.3), 105 (7.7), 91 (14.1), 79 (9.0), 69 (18.9), 55 (8.8).

Isolation and Purification of Natural Robustadial A and B Methyl Ethers. A mixture of the phenolic extract (75 mg) from *E. robusta* (containing mainly robustadials A, B, C, and D; provided by Prof. Snyder), K_2CO_3 (100 mg), and CH_3I (0.2 mL) in acetone (5 mL) was boiled under reflux with stirring for 14 h, then cooled to room temperature, and filtered, and the K_2CO_3 residue was washed with acetone (2 mL). The combined filtrate and washings were concentrated on a Rotavapor. The residue thus obtained contained at least 12 compounds (a portion was analyzed by HPLC on a Whatman partisil column eluted with 0.3% 2-propanol in CH_2Cl_2). The remaining mixture was separated by preparative TLC (20% ethyl acetate and hexanes). One of six bands contained a mixture of two products which were chromatographically identical with the synthetic robustadial A and B methyl ethers. The naturally derived methyl ethers were further separated by reverse-phase HPLC (Waters Bondapak C-18 column, 35% H_2O in CH_3CN) and their identities confirmed by ^{1}H NMR comparison with spectra of the natural derivatives provided by Professor Snyder. Robustadial A dimethyl ether (9 mg): UV λ_{max} 262 (ϵ 18 300), 282 (11 800), 326 nm (3500); CD (methanol) 212 ($\Delta\epsilon$ -5.40), 256 (+4.27), 275 (+1.88), 320 (+1.51), 354 nm (-0.91); $[\alpha]^{20}$ = +62.2° (*c* 0.45, methanol); ^{1}H NMR δ 0.89 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.97 (s, 3 H), 1.20 (s, 3 H), 1.26 (m, H), 1.46–2.37 (12 H), 2.95 (m, H), 3.82 (s, 3 H), 3.90 (s, 3 H), 10.25 (s, H), 10.33 (s, H). Robustadial B dimethyl ether (8.6 mg): UV (methanol) λ_{max} 262 (ϵ 18 000), 282 (11 950), 326 nm (3300); CD (methanol) 227 ($\Delta\epsilon$ -2.61), 255 (-3.42), 292 (+1.21), 330 (+0.50), 354 nm (+0.23); $[\alpha]^{20}$ = -45.1° (*c* 0.43, methanol); ^{1}H NMR δ 0.89 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 1.26 (s, 3 H), 1.27 (m, H), 1.48–2.05 (9 H), 2.10–2.34 (3 H), 2.93 (m, H), 3.83 (s, 3 H), 3.91 (s, 3 H), 10.25 (s, H), 10.34 (s, H).

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Registry No. **1b**, 118100-95-1; **4**, 20628-06-2; **5**, 115481-66-8; **6**, 115463-47-3; **7**, 115510-71-9; **8**, 115586-52-2; **9**, 115463-48-4; **10a**,

115463-49-5; **10b**, 115586-53-3; **10c**, 115463-52-0; **10d**, 115463-53-1; **10e**, 115463-50-8; **10f**, 88130-99-8; **11a**, 115510-72-0; **11b**, 115463-55-3; **11c**, 115510-75-3; **11d**, 115510-76-4; **11e**, 115510-73-1; **11f**, 88197-30-2; 4β-H-**12a**, 115510-84-4; 4β-H-**12b**, 115510-85-5; 4β-H-**12c**, 115510-88-8; 4β-H-**12d**, 115510-89-9; 4β-H-**12e**, 115510-86-6; 4α-H-**13a**, 115510-78-6; 4α-H-**13b**, 115510-79-7; 4α-H-**13c**, 115510-82-2; 4α-H-**13d**, 115510-83-3; 4α-H-**13e**, 115510-80-0; (+)-nopinone, 38651-65-9.

Chiral Synthesis via Organoboranes. 21. Allyl- and Crotylboration of α-Chiral Aldehydes with Diisopinocampheylboron as the Chiral Auxiliary

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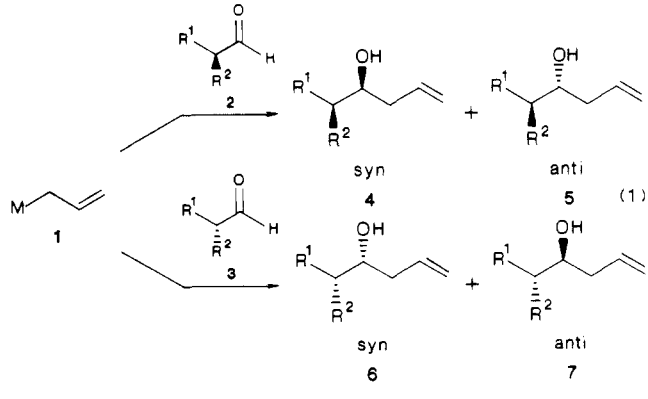
B-Allyldiisopinocampheylboranes [**18**, prepared from (+)-α-pinene; **19**, prepared from (−)-α-pinene] have been screened for diastereofacial selectivity in their reaction with α-substituted chiral aldehydes. Both syn and anti products have been obtained in very high diastereoselectivities. Further, (*E*)-crotyldiisopinocampheylboranes [**20**, prepared from (+)-α-pinene; **21**, prepared from (−)-α-pinene] and (*Z*)-crotyldiisopinocampheylboranes [**22**, prepared from (+)-α-pinene; **23**, prepared from (−)-α-pinene] have been used for diastereofacial selectivity in their reaction with α-substituted chiral aldehydes. These crotylboranes, **20–23**, are highly diastereoselective reagents and the corresponding (3,4- and 4,5)-anti,syn, -anti,anti, and -syn,anti products have been obtained in very high facial selectivities; even the syn,syn product has been obtained in moderately good facial selectivity. Finally, the relative efficiencies of the various chiral auxiliaries utilized in the literature for the allyl- and crotylboration have been compared with those achieved by the diisopinocampheylboron moiety.

The reaction of allylic organometallic reagents and enolate equivalents with carbonyl compounds, the utility of the resulting alcohols in the construction of complex molecules, and their essential feature as biosynthetic intermediates have been amply demonstrated.[2-5] Many allylic organometallic reagents (allyl-M, such as M = Li, B, Si, Sn, etc.) react smoothly with carbonyl compounds to yield the corresponding homoallylic alcohols.[6] Reactions of this type have significant advantages over enolate-derived products in that the newly formed alkenes may be readily transformed into aldehydes and the operation repeated. In addition, the alkenes may be selectively epoxidized, thus readily introducing a third chiral center. Our objective for research in this area, required to support applications in natural products synthesis, is the development of methodology and/or reagents suitable for the synthesis of each diastereomeric relationship with exceptional selectivity and control. Although considerable effort has been devoted to the elucidation of the stereochemistry of the reactions of allylic organometallic compounds with achiral aldehydes, only recently have studies begun in earnest to probe the factors influencing aldehyde diastereofacial selectivity. Consequently, the full potential of allylic metal compounds in acyclic stereoselective synthesis is far from realized.

Like enolates, allylorganometallic reagents react with α-substituted chiral aldehydes to furnish diastereomeric mixtures of syn (**4** and **6**) and anti (**5** and **7**) alcohols (eq 1). This transformation generates two new stereochemical



(1)

relationships and, potentially, four diastereomeric products. Similarly, crotyl organometallic reagents react with chiral aldehydes to furnish diastereomeric mixtures of (3,4- and 4,5)-anti,syn (**10** and **12**), -anti,anti (**11** and **13**), -syn,anti (**15** and **17**), and -syn,syn (**14** and **16**) alcohols (eq 2).

Thus, this transformation generates three new stereochemical relationships and potentially eight diastereomeric

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